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High-Pressure Promoted Stereoselective Tandem [4+2]/[3+2] Cycloadditions of Nitroalkenes and Enol Ethers

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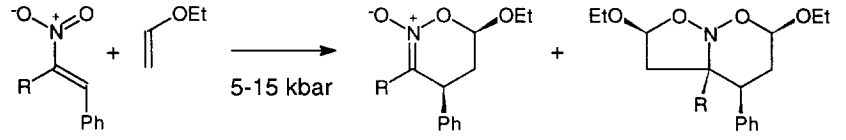
Abstract: Tandem [4+2]/[3+2] cycloadditions of nitrostyrene and 1-phenyl-2-nitropropene with ethyl vinyl ether or 2,3-dihydrofuran are strongly accelerated under high pressure. Mono [4+2] cycloadducts and tandem [4+2]/[3+2] cycloadducts were obtained. Furthermore, the *in situ* formed mono adduct reacts selectively with methyl acrylate in a one-pot reaction to give a three-component [4+2]/[3+2] cycloadduct. Employing high pressure eliminates the need for stoichiometric amounts of Lewis acid catalysts, large amounts of enol ethers or long reaction times, which are necessary at ambient pressure.

In the past few years, much attention has been paid to tandem [4+2]/[3+2] cycloadditions of nitroalkenes, e.g. by Denmark *et al.*[1-5] In this type of reaction, a nitroalkene is allowed to react with an electron-rich alkene in an inverse electron demand Diels-Alder reaction, thus forming a nitronate which then reacts with a second alkene in a [3+2] cycloaddition, leading to a nitroso acetal. Nitroso acetals have interesting synthetic potential as intermediates in the synthesis of biologically active pyrrolizidine alkaloids[5]. Generally, these reactions are performed in the presence of a stoichiometric quantity of Lewis acid catalyst. Without a catalyst, the reaction requires a large excess (90 eq.) of enol ether[6-8], long reaction times[6] or a strongly activated nitroalkene[9,10].

It is generally known that cycloadditions are accelerated by high pressure[11]. Therefore, we rationalized that high pressure would allow short reaction times and eliminate the need for a catalyst and a large excess of enol ethers. Furthermore, the scope of the reaction might be extended toward sterically more hindered reactants. Since a high pressure effect can be anticipated, reactions of nitrostyrene **1a** or 1-phenyl-2-nitropropene **1b** with 5 or 6 equivalents of ethyl vinyl ether **2**, carried out in chloroform, were investigated at different pressures (5-15 kbar) (scheme 1).



1a R = H
1b R = Me

2

3a R = H
3b R = Me

4a R = H
4b R = Me

Scheme 1.

For comparison, the reaction of **1a** with **2** was also carried out at ambient pressure, in the presence of a large excess[12] of **2**. This reaction required five days to give complete conversion of **1a**, mainly to the tandem adduct **4a**, which was isolated by column chromatography. The mono adduct **3a** could not be isolated,

probably because of its instability on silica gel. However, this reaction was strongly promoted by high pressure (10 kbar) and gave complete and clean conversion of **1a** in only one hour. The pressure-dependent conversion of mono and tandem adduct, as determined by NMR, is presented in table 1. These results show also that high pressure has a minor influence on the ratio of mono adduct/tandem adduct, and that the tandem adduct is always the main product.

Table 1. Ratio of mono adduct **3a** and tandem adduct **4a** formed after 1 hour at various pressures (as determined by NMR[13])

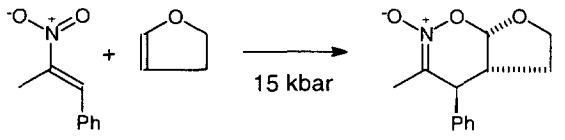
p (kbar)	conversion (%)	ratio **3a/4a**
5	35	0.2
8	85	0.16
10	100	0.17
12	100	0.19

The less reactive **1b** gave, after seven days at ambient pressure and in the presence of a large excess[12] of **2**, only 50% conversion, mainly to the mono adduct **3b**. The results obtained at high pressure (10 and 15 kbar) are presented in table 2. At 15 kbar, within two hours and using only 5 eq. of **2**, complete and almost exclusive conversion of **1b** to the tandem adduct **4b** was observed. At lower pressure (10 kbar), complete conversion was observed after 23 hours. Interestingly, at lower pressure (10 kbar), the mono adduct **3b** was isolated in good yield after two hours.

Table 2. Ratio of mono adduct **3b** and tandem adduct **4b** in time at 10 and 15 kbar (as determined by NMR[13])

p (kbar)	t (h)	conversion (%)	ratio **3b/4b**
10	2	90	2.6
10	23	100	0.25
10	40	100	0.05
15	2	100	0.05

To investigate the steric scope of this reaction further, we examined the reaction of **1b** with the more sterically hindered 2,3-dihydrofuran **5** (scheme 2). At ambient pressure, the reaction of **1b** with 7 eq. of **5** gave less than 10% conversion after 65 hours. After 19 hours in acetonitrile at 15 kbar, the reaction of **1b** with 7 eq. of **5** gave 60% mono adduct **6**. No formation of a tandem adduct was observed.



1b **5** **6**

Scheme 2.

The regio- and stereochemistry of the formation of the mono and tandem adducts was determined by NMR spectroscopy (COSY and NOESY experiments on isolated products). These results show that the [4+2] addition of both **1a** and **1b** with ethyl vinyl ether **2** have taken place entirely regio- and *endo*-selective (figure 1), whilst the subsequent [3+2] addition proceeded with complete regio- and *exo* selectivity, and *anti* with respect to the phenyl group. The monoadduct **6** however, was shown to be the *exo* isomer. This is probably due to the steric hindrance of the five-membered ring of 2,3-dihydrofuran in the *endo* transition state (figure 1).

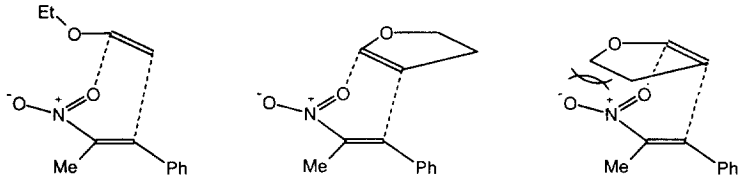
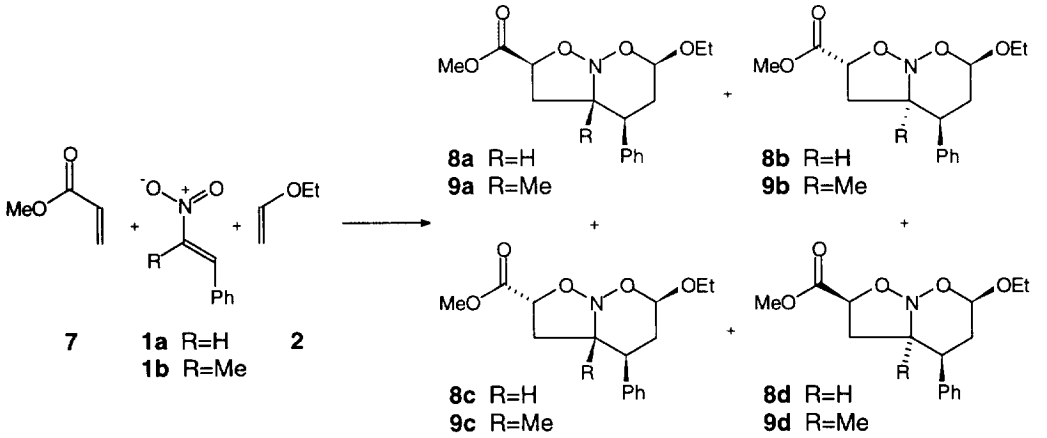


Figure 1. Stereoselective approach of **2** and **5** to **1b**

THREE-COMPONENT TANDEM CYCLOADDITIONS

To explore the synthetic potential of high-pressure tandem cycloadditions further, we investigated the cycloaddition of nitroalkenes with enol ethers in the presence of an electron-poor alkene. It is known from literature that nitronates react faster with electron-poor alkenes than with electron-rich alkenes[7-9,14]. Therefore, the formed nitronate can be intercepted selectively by the electron-poor alkene. This would make it possible to prepare a three-component adduct. Without high pressure, three-component adducts are only formed intramolecularly[1] or from strongly activated electron-poor nitroalkenes[7-9,14]. At high pressure, we explored the reaction of the non-activated nitroalkenes **1a** and **1b** with ethyl vinyl ether **2** and methylacrylate **7** as presented in scheme 3. We chose to employ methyl acrylate **7** as the electron-poor dipolarophile, because this compound does not react with **2** under high pressure.



Scheme 3.

The reaction of **1a**, **2**, and **7** was examined, using **2** and **7** in a fourfold excess. After 1 hour at 15 kbar, 90-95% conversion had taken place (according to NMR), and two main three-component cycloadducts **8b** and **8c** had been formed, which were separated by column chromatography and isolated in 17% and 45% yield, respectively. Consequently, we tried the reaction of **1b**, **2**, and **7** (using only a twofold excess of **2** and **7**). After 19 hours at 15 kbar, three main products **9a**, **9b** and **9c** were isolated after column chromatography in a yield of 29%, 18% and 29%, respectively. Diastereomer **9d** was not formed.

The regiochemistry and relative stereochemistry of the formation of these products were elucidated by COSY and NOESY experiments. Again, the [4+2] cycloaddition of nitroalkenes **1a** and **1b** with **2** proceeded with complete regio- and *endo*-selectivity. The subsequent [3+2] cycloadditions of the nitronate with **7** were completely regioselective but gave a mixture of *exo-anti* (**9a**), *exo-syn* (**8b**,**9b**) and *endo-anti* (**8c**,**9c**) isomers (*anti* and *syn* with respect to the phenyl group). The found regioselectivity in the [3+2] cycloadditions is in agreement with reported literature data of related cycloadditions of acrylates with nitrones and nitronates[15]. The absolute configuration in scheme 3 was arbitrarily chosen.

EXPERIMENTAL SECTION

Chloroform was purified by eluting 150 ml over 10 g basic alumina. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AC-300 (300 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer in $CDCl_3$ with TMS as internal standard. Melting points were measured with a Büchi melting point determining apparatus. The high pressure apparatus operating at 1-15 kbar has been described before[16]. Purification of products was done by flash column chromatography on silica gel. TLC analyses were performed using silica gel (Merck DC-Fertigplatten Kieselgel 60F-254). Mass spectra were recorded on a VG 7060E spectrometer.

General Procedure for the high-pressure tandem [4+2]/[3+2] cycloaddition of nitroalkenes with enol ethers: The prescribed amount of nitroalkene was dissolved in 5-6.6 eq. of the enol ether, which was then diluted with an appropriate solvent to a 1.5 ml volume in a teflon tube. The closed tube was placed at the reported pressure for the reported time. After depressurizing, the reaction mixture was concentrated *in vacuo* and the products were separated by column chromatography over silica gel using ethyl acetate/*n*-hexane mixtures as eluent.

6-ethoxy-3-methyl-4-phenyl-5,6-dihydro-4*H*-[1,2]-oxazine-*N*-oxide (3b)

Prepared according to the general procedure from 163 mg (1 mmol) **1b** and 377 mg (5.2 mmol) **2** in chloroform. White solid, m.p. 58-59°C, R_f (1:1 ethyl acetate:*n*-hexane v/v): 0.15. EI-MS: calcd. for $C_{13}H_{17}NO_3$: m/z=235, found (rel. int.): 235 (M^+, 1.4), 218 (8.5), 205 (27.5), 159 (11.6), 133 (18.8), 131 (27.2), 115 (34.9), 105 (62.5), 91 (46.7), 72 (ethyl vinyl ether, 100). Peak Match: calcd. 235.12084, found 235.12096 ± 0.00092. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm), J (Hz): 7.36-7.22 (5H, m, Ph), 5.38 (1H, dd, J=4.0, J=5.1, H-6), 4.10 (1H, dq, J_q=7.1, J_d=9.5, C<u>H</u>HO), 3.75 (1H, t, J=8.1, H-4), 3.69 (1H, dq, J_q=7.0, J_d=9.5, CH<u>H</u>O), 2.56 (1H, ddd, J=4.2, J=8.66, J=14.0, H-5), 2.11 (1H, ddd, J=5.4, J=7.2, J=14.0, H'-5), 1.88 (3H, d, J=1.1, C<u>H</u>$_3$C), 1.25 (3H, t, J=7.1, C<u>H</u>$_3$CH$_2$). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm): 140.0 (C-*ipso*), 128.9 (C-*ortho*), 128.4 (C-*meta*), 127.6 (C-*para*), 124.13 (C-3), 102.2 (C-6), 65.5 (CH$_3$<u>C</u>H$_2$O), 42.3 (C-4), 35.2 (C-5), 17.2, 14.9 (<u>C</u>H$_3$ (2×)).

2,6-diethoxy-4-phenyl-hexahydro-isoxazolo[2,3-*b*][1,2]-oxazine (4a)

Prepared according to the general procedure from 149 mg (1 mmol) **1a** and 374 mg (5.2 mmol) **2** in chloroform. Oil, R_f (1:5 ethyl acetate:*n*-hexane v/v): 0.24. EI-MS: calcd. for $C_{16}H_{23}NO_4$: m/z=293, found (rel. int.): 293 (M^+, 0.1), 276 (0.48), 248 (M^+–OEt, 16.4), 202 ($C_{12}H_{12}NO_2^+$, 17.8), 191 (65.1), 161 (22.9), 143 (77.4), 117 (100), 104 (65). Peak Match: calcd. 293.1627, found 293.1627 ± 0.0011. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm), J (Hz): 7.33-7.24 (5H, m, Ph), 5.65 (1H, dd, J=4.2, J=1.6, H-2), 4.92 (1H, t, J=7.4, H-6), 4.03 (1H, dq, J_q=7.1, J_d=9.5, C<u>H</u>HO), 3.84 (1H, t, J=7.7, H-3a), 3.78 (1H, dq, J_d=9.5, J_q=7.1, CH<u>H</u>O), 3.57 (1H, dq, J_q=7.1, J_d=9.5, C'<u>H</u>'H'O'), 3.46 (1H, dq, J_q=7.1, J_d=9.4, C'H'<u>H</u>'O'), 2.81 (1H, ddd, J=3.6, J=7.9, J=13.9, H-4), 2.34-2.22 (3H, m, H-3, H'-3, H-5), 2.09 (1H, ddd, J=3.6, J=6.8, J=13.5, H'-5), 1.29 (3H, t, J=7.1, C<u>H</u>$_3$), 1.13 (3H, t, J=7.1, C<u>H</u>$_3$). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm): 141.7 (C-*ipso*), 128.8 (C-*ortho*), 127.4 (C-*meta*), 127.1, (C-*para*), 107.5 (C-2), 100.0 (C-6), 72.7 (C-3a), 64.0, 63.5 (CH_2O (2×)), 43.5 (C-4), 37.7, 33.2 (C-3, C-5), 15.1, 14.9 (CH_3 (2×)).

2,6-diethoxy-3a-methyl-4-phenyl-hexahydro-isoxazolo[2,3-*b*][1,2]-oxazine (4b)

Prepared according to the general procedure from 163 mg (1 mmol) **1b** and 377 mg (5.2 mmol) **2** in deuterochloroform. Oil, R_f (1:5 ethyl acetate:*n*-hexane v/v): 0.28. CI-MS: calcd. for $C_{17}H_{25}NO_4$: m/z=307, found (rel. int.): 308 (M+1, 1.9), 290 (0.55), 262 (M–OEt, 28.3), 205 (87.5), 157 (97.9), 146 (30.5), 131 (100). Peak Match: calcd. 307.1784, found 307.1783 ± 0.0015. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm), J (Hz): 7.35-7.14 (5H, m, Ph), 5.79 (1H, dd, J=1.3, J=6.8, H-2), 4.93 (1H, dd, J=6.7, J=8.14, H-6), 4.04 (1H, dq, J_d=9.6, J_q=7.1, CH<u>H</u>O), 3.81 (1H, dq, J_d=9.6, J_q=7.1, CH<u>H</u>O), 3.63-3.47 (2H, m, C<u>H</u>HO (2×)), 3.14 (1H, dd, J=2.6, J=14.0, H-4), 2.65 (1H, dd, J=6.9, J_{gem}=12.6, H-3), 2.32 (1H, dt, J_d=8.2, J_t=13.7, H-5), 2.16 (1H, dd, J=1.4, J_{gem}=12.6, H'-3), 2.05 (1H, ddd, J=2.7, J=6.6, J_{gem}=13.4, H'-5), 1.29 (3H, t, J=7.1, C<u>H</u>$_3$CH$_2$), 1.17 (3H, t, J=7.1, C'<u>H</u>'$_3$C'H'$_2$), 0.86 (3H, s, CH$_3$C). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm): 139.6 (C-*ipso*), 128.4 (C-*ortho*), 127.9 (C-*meta*), 127.0 (C-*para*), 109.9 (C-2), 100.3 (C-6), 75.1 (C-3a), 65.0, 63.7 (<u>C</u>H$_2$O (2×)), 47.1 (C-4), 45.0, 30.0 (C-3, C-5), 19.0, 15.2, 15.1 (<u>C</u>H$_3$ (3×)).

3-methyl-4-phenyl-4a,5,6,7a-tetrahydro-4*H*-furo[3,2-*e*][1,2]oxazine-*N*-oxide (6)

Prepared according to the general procedure from 165 mg (1 mmol) **1b** and 463 mg (6.6 mmol) **5** in acetonitrile. White solid, m.p. 130-133°C, R_f (1:1 ethyl acetate:*n*-hexane v/v): 0.08. EI-MS: calcd. for $C_{13}H_{15}NO_3$: m/z=233, found (rel. int.): 233 (M^+, 2.1), 216 (14.0), 203 (5.4), 115 (22.3), 91 (23.7), 77 (C_6H_5, 10.3), 70 (dihydrofuran, 100). Peak Match: calcd. 233.10519, found 233.10515 ± 0.00092. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm), J (Hz): 7.41-7.22 (5H, m, Ph), 5.88 (1H, d, J=5.9, H-7a), 4.20 (1H, q, J=7.7, H-6), 3.99 (1H, dt, J_d=5.7, J_t=8.3, H'-6), 3.71 (1H, d, J=3.7, H-4), 3.01 (1H, ddt, J_d=9.4, J_d=3.5, J_t=6.1, H-4a), 2.31 (1H, m, H-5), 2.04 (3H, s, CH_3), 1.95-1.85 (1H, m, H'-5). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm): 138.1 (C-*ipso*), 129.1 (C-*ortho*), 127.8 (C-*para*), 127.7 (C-*meta*), 124.3 (C-3), 106.7 (C-7a), 68.4 (C-6), 48.1, 45.9 (C-4, C-4a), 30.6 (C-5), 17.9 (CH_3).

<u>General Procedure for the high-pressure three-component one-pot tandem cycloaddition</u>: The prescribed amount of nitroalkene was dissolved in 2 or 4 eq. of the enol ether and 2 or 4 eq. of methyl acrylate. The solution was then diluted with chloroform to a 15 ml volume in a teflon tube. The closed tube was placed at

the reported pressure for the reported time. After depressurizing, the reaction mixture was concentrated *in vacuo* and the products were separated by column chromatography over silica gel using ethyl acetate/*n*-hexane mixtures as eluent.

methyl 6-ethoxy-4-phenyl-hexahydro-isoxazolo[2,3-*b*][1,2]-oxazine-2-carboxylate (8b and 8c)

Prepared according to the general procedure from 402 mg (2.7 mmol, 1 eq.) **1a**, 778 mg (10.8 mmol, 4 eq.) **2** and 929 mg (10.8 mmol, 4 eq.) **7** in chloroform.

Compound **8b**: Oil, R_f (1:1 ethyl acetate:*n*-hexane v/v): 0.50. EI-MS: calcd. for $C_{16}H_{21}NO_5$: m/z=307, found (rel. int.): 288 (0.43), 277 (0.32), 262 (M^+–OEt, 1.2), 248 (3.25), 231 (9.0), 205 (M^+–CH_3O-COCO-CH_3, 79.8), 171 (15.7), 161 (11.6), 145 (45.2), 143 (36.1), 129 (27.1), 117 (100), 105 (40.2). Peak Match: calcd. for $C_{14}H_{16}NO_4$ (M–EtO^-): 262.10793, found 262.10789 ± 0.00076. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm), J (Hz): 7.38-7.21 (5H, m, Ph), 5.06 (1H, dd, J=3.2, J=10.4, H-2), 4.88 (1H, dd, J=2.2, J=9.3, H-6), 4.08-4.00 (1H, m, C<u>H</u>HO), 3.82-3.57 (3H, m, H-3a, H-4, CH<u>H</u>O), 3.70 (3H, s, C<u>H</u>$_3$O), 2.62 (1H, q, J=11.4, H-3), 2.08-1.88 (2H, m, H-5), 1.73 (1H, ddd, J=3.2, J=7.2, J=12.1, H'-3), 1.26 (3H, t, J=7.0, C<u>H</u>$_3$CH$_2$). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm): 170.7 (C=O), 139.3 (C-*ipso*), 128.8 (C-*ortho*), 127.3 (C-*para*), 127.1 (C-*meta*), 100.1 (C-2), 80.5 (C-6), 71.5 (C-3a), 65.3 (CH_3<u>C</u>H$_2$), 52.3, 38.0 (CH_3O, C-4), 29.8, 28.6 (C-3, C-5), 15.0 (<u>C</u>H$_3$CH$_2$).

Compound **8c**: White solid, m.p. 97-99°C, R_f (1:1 ethyl acetate:*n*-hexane v/v): 0.45. EI-MS: calcd. for $C_{16}H_{21}NO_5$: m/z=307, found (rel. int.): 288 (0.09), 277 (0.29), 262 (M^+–OEt, 0.71), 248 (0.89), 231 (7.2), 205 (M^+–CH_3O-COCO-CH_3, 92.3), 171 (11.8), 161 (19.5), 145 (16.9), 143 (46.3), 129 (37.4), 117 (100), 105 (51.9). Peak Match: calcd. for $C_{14}H_{16}NO_4$ (M–EtO^-): 262.10793, found 262.1076 ± 0.0010. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm), J (Hz): 7.37-7.23 (5H, m, Ph), 4.94 (1H, t, J=7.3, H-2), 4.77 (1H, t, J=8.1, H-6), 4.02 (1H, dq, J_q=7.1, J_d=9.6, C<u>H</u>HO), 3.82 (3H, s, C<u>H</u>$_3$O), 3.67 (1H, q, J=8.3, H-3a), 3.55 (1H, dq, J_q=7.1, J_d=9.6, CH<u>H</u>O), 2.94 (1H, ddd, J=3.9, J=7.7, J=13.9, H-4), 2.68-2.56 (2H, m, H-3), 2.22 (1H, dt, J_d=8.1, J_t=13.6, H-5), 2.07 (1H, ddd, J=3.9, J=6.7, J=13.6, H'-5), 1.27 (3H, t, J=7.1, C<u>H</u>$_3$CH$_2$). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm): 171.2 (C=O), 141.6 (C-*ipso*), 128.8 (C-*ortho*), 127.3 (C-*meta*), 127.2, (C-*para*), 99.9 (C-2), 81.4 (C-6), 75.4 (C-3a), 63.5 (CH_3<u>C</u>H$_2$), 52.5, 43.8 (C-4, <u>C</u>H$_3$O), 34.3, 33.2 (C-3, C-5), 15.0 (<u>C</u>H$_3$CH$_2$).

methyl 6-ethoxy-3a-methyl-4-phenyl-hexahydro-isoxazolo[2,3-*b*][1,2]-oxazine-2-carboxylate (9a, 9b, 9c)

Prepared according to the general procedure from 326 mg (2.0 mmol, 1 eq.) **1b**, 288 mg (4.0 mmol, 2 eq.) **2** and 344 mg (4.0 mmol, 2 eq.) **7** in chloroform.

Compound **9a**: White solid, m.p. 98-100°C, R_f (1:1 ethyl acetate:*n*-hexane v/v): 0.52. EI-MS: calcd. for $C_{17}H_{23}NO_5$: m/z=321, found (rel. int.): 321 (M^+, 0.22), 289 (0.55), 276 (M^+–OEt, 0.84), 262 (1.7), 245 (13.0), 219 (M^+–CH_3O-COCO-CH_3, 84.6), 185 (10.7), 157 (62.7), 143 ($C_6H_9NO_3^+$, 25.0), 131 (100), 104 (56.9), 91 (34.2). Peak Match: calcd. 321.15762, found 321.15776 ± 0.00091; calcd. for $C_{13}H_{15}O_3$: 219.10212, found 219.10213 ± 0.00088. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm), J (Hz): 7.35-7.15 (5H, m, Ph), 5.23 (1H, q, J=5.3, H-2), 4.98 (1H, dd, J=6.7, J=8.0, H-6), 4.01 (1H, dq, J_q=7.1, J_d=9.6, CH<u>H</u>O), 3.75 (3H, s, CH_3O), 3.58 (1H, dq, J_q=7.1, J_d=9.6, C<u>H</u>HO), 3.23 (1H, dd, J=14.0, J=2.7, H-4), 2.80 (1H, t, J=11.3, H-3), 2.37 (1H, dd, J=5.3, J=12.1, H'-3), 2.31 (1H, dt, J_d=8.3, J_t=13.7, H-5), 2.06 (1H, ddd, J=2.8, J=6.7, J=13.3, H'-5), 1.29 (3H, t, J=7.1, C<u>H</u>$_3$CH$_2$), 0.76 (3H, s, C<u>H</u>$_3$C). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm): 170.5 (C=O), 139.2

(C-*ipso*), 128.3 (C-*ortho*), 127.7 (C-*meta*), 127.0 (C-*para*), 100.0 (C-2), 81.4 (C-6), 77.2 (C-3a), 63.4 ($CH_3\underline{C}H_2$), 52.3, 46.9 (C-4, CH_3O), 42.9, 30.0 (C-3, C-5), 19.9 ($\underline{C}H_3C$), 14.9 ($\underline{C}H_3CH_2$).

Compound **9b**: Oil, R_f (1:1 ethyl acetate:*n*-hexane v/v): 0.55. EI-MS: calcd. for $C_{17}H_{23}NO_5$: m/z=321, found (rel. int.): 321 (M^+, 0.07), 291 (0.60), 276 (M^+–OEt, 1.8), 262 (2.5), 245 (35.5), 219 (M^+–CH_3O-COCO-CH_3, 94.4), 185 (21.8), 157 (59.4), 143 (32.9), 131 (100), 104 (55.6), 91 (47.11). Peak Match: calcd. 321.15762, found 321.15776 ± 0.00091; calcd. for $C_{13}H_{15}O_3$: 219.10212, found 219.10213 ± 0.00088. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm), J (Hz): 7.35-7.21 (5H, m, Ph), 5.20 (1H,dd, J=3.7, J=11.0, H-2), 4.88 (1H, dd, J=2.0, J=9.5, H-6), 4.03 (1H, dq, J_q=7.1, J_d=9.6, C$\underline{H}$HO), 3.73 (3H, s, CH_3O), 3.67 (1H, dq, J=7.1, J=9.6, CH$\underline{H}$O), 3.16 (1H, dd, J=4.7, J=13.2, H-4), 3.01 (1H, t, J=11.5, H-3), 2.05 (1H, dt, J_t=13.2, J_d=9.54, H-5), 1.89 (1H, ddd, J=2.0, J=4.6, J=13.1, H'-5), 1.71 (1H, dd, J=3.7, J=11.9, H'-3), 1.25 (3H, t, J=7.1, $C\underline{H}_3CH_2$), 1.12 (3H, s, CH_3C). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm): 170.8 (C=O), 139.4 (C-*ipso*), 128.5 (C-*ortho*), 128.4 (C-*meta*), 127.4 (C-*para*), 99.5 (C-2), 80.4 (C-6), 74.7 (C-3a), 65.2 ($CH_3\underline{C}H_2$), 52.3, 46.5 (C-4, CH_3O), 33.5 (C-3, C-5), 24.0 ($\underline{C}H_3C$), 15.1 ($\underline{C}H_3CH_2$).

Compound **9c**: White solid, m.p. 106-109°C, R_f (1:1 ethyl acetate:*n*-hexane v/v): 0.47. EI-MS: calcd. for $C_{17}H_{23}NO_5$: m/z=321, found (rel. int.): 321 (M^+, 0.03), 219 (M^+–CH_3O-COCO-CH_3, 74.8), 185 (16.8), 157 (40.0), 143 (28.2), 131 (100), 105 (43.0). Peak Match: calcd. 321.15762, found 321.15746 ± 0.00091; calcd. for $C_{13}H_{15}O_3$: 219.10212, found 219.10213 ± 0.00088. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm), J (Hz): 7.36-7.16 (5H, m, Ph), 4.95 (1H, dd, J=6.7, J=8.1, H-6), 4.83 (1H, dd, J=7.52, J=9.1, H-2), 4.03 (1H, dq, J_q=7.1, J_d=9.7, C$\underline{H}$HO), 3.83 (3H, s, CH_3O), 3.57 (1H, dq, J_q=7.1, J_d=9.7, CH$\underline{H}$O), 3.25 (1H, dd, J=2.7, J=14.1, H-4), 2.86 (1H, dd, J=7.4, J=12.1, H-3), 2.43 (1H, dd, J=9.1, J=12.1, H'-3), 2.31 (1H, dt, J_t=13.7, J_d=8.2, H-5), 2.05 (1H, ddd, J=2.8, J=6.6, J=13.4, H'-5), 1.28 (3H, t, J=7.1, $C\underline{H}_3CH_2$), 0.72 (3H, s, CH_3C). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm): 171.3 (C=O), 139.2 (C-*ipso*), 128.3 (C-*ortho*), 127.7 (C-*meta*), 126.9 (C-*para*), 100.1 (C-2), 81.8 (C-6), 77.2 (C-3a), 63.5 ($CH_3\underline{C}H_2$), 52.3, 46.6 (C-4, CH_3O), 41.5, 30.2 (C-3, C-5), 19.3 ($\underline{C}H_3C$), 14.9 ($\underline{C}H_3CH_2$).

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For compound **3a**, the singlet at δ = 6.28 ppm was ascribed to H-3 (N=C–H).
For compound **3b**, the double doublet at δ = 5.38 ppm (H-6) was used.
For compound **4a**, the double doublet at δ = 5.65 ppm (H-2) was used.
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